

Dean L. Engelhardt, et al.
Serial No.: 08/486,069

Filed: June 7, 1995

Page 2 [Supplemental Amendment to Applicants' May 23, 2000 Amendment

Under 37 C.F.R. §1.115 - June 19, 2000]



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TECH CENTER 1600/2900

KINDLY AMEND THE ABOVE-IDENTIFIED APPLICATION AS FOLLOWS:

In The Claims:

Please amend claims 500, 506, 716, 721, 738, 859, 872, 873, 890, 1011, 1012, 1024, 1025, 1042, 1163, 1164, 1176, 1177, 1197, 1198, 1235, 1281, 1298, 1393, 1411, 1453, 1573, 1582, 1693, 1701, 1702, 1703 and 1704 as follows:

Sub X1 569. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

S1 providing or generating detectable labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

subjecting said detectable labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting non-radioactively the presence of each of said separated or resolved fragments by means of said modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

Sub Y2 586. (Amended) The process according to claim 569, wherein the detectable labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

S2 716. (Amended) The process according to claims 569, 600 or 601, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.



Sub X10 721. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or a portion thereof wherein each of said fragments comprises one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more modified nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

introducing or subjecting said detectable labeled fragments to a sequencing gel;

separating or resolving said fragments in said sequencing gel; and

detecting non-radioactively each of the separated or resolved fragments; and determining the sequence of said nucleic acid of interest.

Sub X11 738. (Amended) The process according to claim 721, wherein the detectable labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

Sub X15 859. (Amended) The process according to claim 721, wherein said detectable labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

Sub X19 872. (Amended) The process according to claim 721, wherein said detecting step comprises localizing said detectable labeled nucleic acid fragments by means of said one or more modified or labeled nucleotides or nucleotide analogs.



873. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

S4
detecting non-radioactively the detectable labeled nucleic acid fragments with a sequencing gel; and

determining the sequence of said nucleic acid of interest.

Sub 10
S8
890. (Amended) The process according to claim 873, wherein the detectable labeled complementary nucleic acid is fragmented and separated prior to detecting in said sequencing gel.

Sub 11
X24
1011. (Amended) The process according to claim 873, wherein said detectable labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

S9

1012. (Amended) The process according to claim 873, wherein said detecting step, the detectable labeled nucleic acid fragments are separated or resolved electrophoretically.

Sub X28
S10
1024. (Amended) The process according to claim 873, wherein said detecting step comprises localizing said detectable labeled nucleic acid fragments by means of said one or more modified or labeled nucleotides or nucleotide analogs.



S10
~~1025. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting non-radioactively with a sequencing gel one or more detectable labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more modified or labeled nucleotides or nucleotide analogs have been modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.~~

SUB 1025
S11 X
~~1042. (Amended) The process according to claim 1025, wherein the detectable labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.~~

S12
SUB 1025
~~163. (Amended) The process according to claim 1025, wherein said detectable labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.~~

SUB 1025
~~1164. (Amended) The process according to claim 1025, wherein said detecting step, the detectable labeled nucleic acid fragments are separated or resolved electrophoretically.~~

S13
SUB 1025
~~1176. (Amended) The process according to claim 1025, wherein said detecting step comprises localizing said detectable labeled nucleic acid fragments by means of said one or more modified or labeled nucleotides or nucleotide analogs.~~

~~1177. (Amended) A process for determining with a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid of interest or a portion thereof, said process comprising the steps of:~~



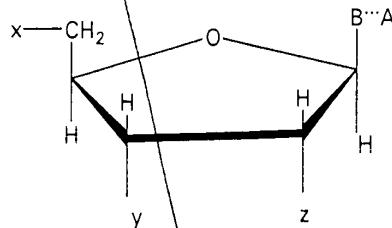
(A) providing

- (i) one or more detectable chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid; or
- (ii) one or more oligonucleotides or polynucleotides comprising at least one said detectable chemically modified or labeled nucleotide or nucleotide analog; or
- (iii) both (i) and (ii);

wherein said chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, and wherein said chemically modified or labeled nucleotides or nucleotide analogs have been modified or labeled non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one chemically modified or labeled nucleotides or nucleotide analogs (ii), or both (i) and (ii), into one or more nucleic acid fragments, to prepare detectable labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof and said one or more chemically modified or labeled nucleotides or nucleotide analogs, and wherein said chemically modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i)



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wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1-

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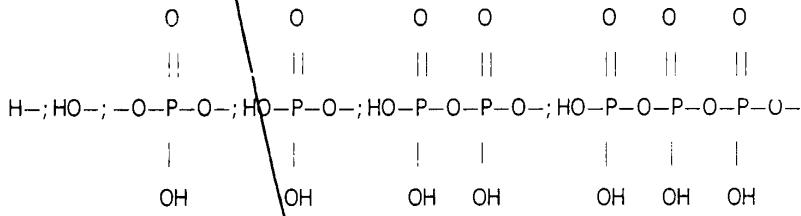
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position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever D is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

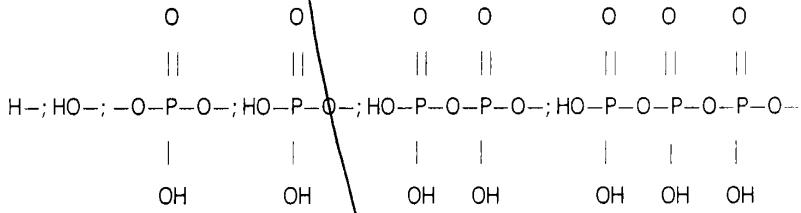
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and HO-;

(ii)

S13

Sig

|
PM-SM-BASE

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C122

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said detectable labeled fragments to a sequencing gel;

(D) separating or resolving said detectable labeled fragments; and

(E) non-radioactively detecting directly or indirectly the presence of said detectable labeled fragments.

S13
curve

S14

1197. (Amended) The process according to claim 1177, wherein the detectable labeled nucleic acid fragments prepared by said incorporating step comprises at least one internal modified nucleotide.

1198. (Amended) The process according to claim 1177, wherein the detectable labeled nucleic acid fragments prepared by said incorporating step comprises at least one terminal modified nucleotide.



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1235. (Amended) The process according to claim 1177, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) comprises a member selected from the group consisting of an olefinic bond at the α -position relative to the point of attachment to the nucleotide, $\pm [-\text{CH}_2\text{NH}-] -\text{CH}_2\text{NH}-$ moiety, or both.

Sub X 37)
S16

1281. (Amended) The process according to claim 1177, wherein said detectable labeled nucleic acid fragment or fragments are terminally ligated or attached to a polypeptide.

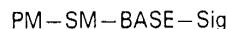
S17

1298. (Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

Sub X 40)

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more detectable oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog



thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

(iii) a nucleotide or nucleotide analog having the formula

Sig

|
PM – SM – BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig – PM – SM – BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

SIN



(b) detecting non-radioactively the presence of said Sig detectable non-radioactive moieties in any of the detectable oligo- or polynucleotides which have hybridized to said nucleic acid of interest.

1393. (Amended) The process according to claim 1298, wherein the [oligo- or] oligo- or polynucleotide is terminally ligated or attached to a polypeptide.

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1411. (Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

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(A) providing:

Sub
X45

(i) an oligo- or polynucleotide having two segments:

(a) a first segment complementary to and capable of specifically hybridizing to a portion of said nucleic acid of interest; and

(b) a second segment comprising at least one protein binding nucleic acid sequence; and

(ii) a detectable protein which is capable of binding to said protein binding nucleic acid sequence;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said detectable protein (ii) to form a complex;

(C) detecting non-radioactively the presence of said detectable protein in said complex and said nucleic acid of interest.

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1453. (Amended) The process according to claim 1446, wherein said signaling component or indicator molecule comprises a monosaccharide, polysaccharide or an oligosaccharide.

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1573. (Amended) The process according to claim 1475, wherein each of [said.] said set of clones or DNA fragments or oligo- or polynucleotides is labeled with the same indicator molecule.

Sub X57

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1582. (Amended) A process for preparing a detectable non-radioactively labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:



(1) one or more detectable chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signaling moieties which are capable of providing directly or indirectly a detectable non-radioactive signal; or

(2) an oligo- or polynucleotide of interest comprising one or more said detectable chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides;

wherein said chemically modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog, and are selected from the group consisting of:

(i)

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a

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position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii)

Sig

PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

[Sig.] Sig is detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached SM, and Sig is covalently attached to PM directly or through a linkage group; and

said oligo- or polynucleotide of interest; and

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(B) either incorporating said one or more modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

S²²
S²³
1693. (Amended) The process according to claim 1690, wherein said Sig comprises a ligand [and.] and the polypeptide comprises an antibody thereto.

S²⁴
sub X⁶⁶
1701. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of providing a detectable radioactive signal, and wherein said one or more modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

introducing or subjecting said fragments to a sequencing gel;
separating or resolving said fragments in said sequencing gel; and
detecting each of the separated or resolved fragments by means of the detectable radioactive signal provided by said chelating compounds or chelating components in the modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

1702. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide



analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of providing a detectable radioactive signal, and wherein said one or more modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

detecting the detectable labeled nucleic acid fragments with a sequencing gel; and

determining the sequence of said nucleic acid of interest.

1703. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting with a sequencing gel one or more detectable labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of providing a detectable radioactive signal, and wherein said one or more modified nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.

1704. (Amended) A process for determining in a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid sequence of interest or a portion thereof, said process comprising the steps of:

(A) providing

- (i) one or more detectable chemically modified nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid, or
- (ii) one or more oligonucleotides or polynucleotides comprising at least one of said detectable chemically modified nucleotides or nucleotide analogs; or

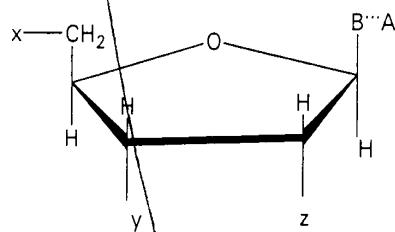
S24



(iii) both (i) and (ii);

wherein said chemically modified nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, wherein said detectable chemically modified nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of providing a detectable radioactive signal, and wherein said chemically modified nucleotides or nucleotide analogs have been modified non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more chemically modified nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one of said chemically modified or labeled nucleotides (ii), or both (i) and (ii), into said one or more nucleic acid fragments, to prepare detectable labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, said labeled fragments further comprising one or more chemically modified nucleotides or nucleotide analogs selected from the group consisting of:



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1' position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

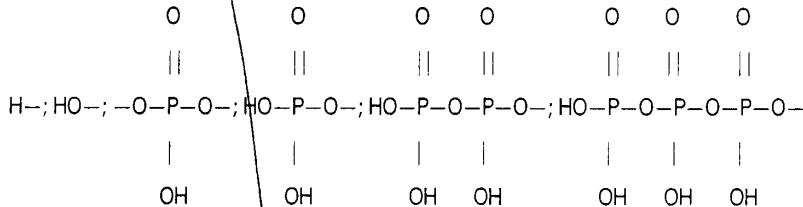
S²⁴



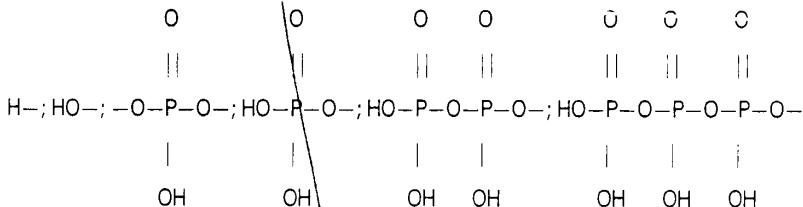
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety comprising a chelating compound or chelating component capable of providing directly or indirectly a detectable radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and HO- [-]

(ii)

Sig
|
PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

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Sig is a signaling moiety comprising a chelating compound or chelating component capable of providing a detectable radioactive signal, and wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig-PM-SM-BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of providing a detectable radioactive signal; and wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

*S24
Coral*

- (C) transferring or subjecting said labeled fragments to a sequencing gel;
- (D) separating or resolving said labeled fragments; and
- (E) detecting directly or indirectly the presence of said labeled fragments.

Please add new claims 1712-1718 as follows:



-- 1712. (NEW) A process for detecting the presence of a nucleic acid of interest in a sample, comprising the steps of:
providing or generating (i) one or more detectable oligonucleotides or polynucleotides, each of said detectable oligonucleotides or polynucleotides comprising a sequence sufficiently complementary to said nucleic acid of interest or to a portion thereof to hybridize thereto, wherein said one or more detectable oligonucleotides or polynucleotides comprise one or more modified or labeled nucleotides or nucleotide analogues, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof, and (ii) a sample that may contain said nucleic acid of interest;
forming in liquid phase hybrids comprising said one or more detectable oligonucleotides or polynucleotides and said nucleic acid of interest;
separating or resolving in a gel said formed hybrids; and
detecting non-radioactively the separated or resolved hybrids. --

SUB X72 S25

-- 1713. (NEW) The process according to claim 1712, wherein after said hybrid forming step, the liquid phase is subjected to nuclease treatment. --

-- 1714. (NEW) The process according to claim 1712, wherein said nucleic acid of interest is selected from the group consisting of DNA, RNA and DNA-RNA. --

-- 1715. (NEW) The process according to claim 1712, wherein said one or more detectable oligonucleotides or polynucleotides are selected from the group consisting of DNA, RNA and DNA-RNA. --

-- 1716. (NEW) The process according to claim 1712, wherein said one or more detectable oligonucleotides or polynucleotides comprise a member selected from the group consisting of biotin, iminobiotin, an electron dense component, a magnetic component, an enzyme, a hormone component, a metal-containing component, a fluorescent component, a chemiluminescent component, an antigen, a hapten, an antibody component and a chelating component. --

SUB (f) 60

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17. (NEW) The process according to claim 1712, wherein said non-radioactive detection step is carried out directly or indirectly. --

SUBJ 1718. (NEW) The process according to claim 1712, wherein said detecting step
is carried out by means of a member selected from the group consisting of
enzymatic measurement, a fluorescent measurement, a phosphorescent
measurement, a chemiluminescent measurement, a calorimetric measurement, a
microscopic measurement and an electron density measurement. --

* * * * *